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Osteosarcoma

Low-Grade Intraosseous-Type Osteosarcoma, Histologically Resembling Parosteal Osteosarcoma, Fibrous Dysplasia, and Desmoplastic Fibroma

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Background. **Low-grade intraosseous osteosarcoma is a rare variety of osteosarcoma and it is difficult to recognize.**

Methods. **A series of 10 patients with low-grade intraosseous osteosarcoma is reported. These patients were identified from the Istituto Rizzoli files, which includes approximately 1000 cases of osteosarcoma. Clinical data and radiographic and histologic features were studied.**

Results. **The radiographic appearance confirmed malignancy in five patients and suggested it in two. A benign lesion was diagnosed in three patients. Three lesions resembled parosteal osteosarcoma, two appeared similar to fibrous dysplasia, and two had features of desmoplastic fibroma. A mixed histologic pattern was found in three other tumors. Recurrence after intralesional excision in all patients indicated the aggressive nature of this lesion. The development of metastases in two patients and progression in the grade of malignancy in one of these highlighted the malignant nature of the tumor.**

Conclusions. **The correct diagnosis would permit adequate treatment with wide surgical margins. *Cancer* 1993; 71:338–45.**

Key words: fibrous dysplasia, low-grade fibrosarcoma, desmoplastic fibroma, solid aneurysmal bone cyst, osteosarcoma.

Low-grade intraosseous-type osteosarcoma (LGIOS) is rare; it is sometimes difficult to recognize it as a low-grade malignant lesion. Histologically, it may resemble parosteal osteosarcoma, fibrous dysplasia, or desmoplastic fibroma. It was found in only 1% of all osteosarcomas recorded in the Rizzoli Institute files and 1.9% of them in the Mayo Clinic files.[1–3] It has a better prognosis than the usual osteosarcoma. It is worthwhile to differentiate it from the more malignant varieties of intraosseous osteosarcomas and from other benign intraosseous lesions with which it can be confused easily. These concepts were summarized in a recent article from the Mayo Clinic that reported on 80 cases of LGIOS.[1] Furthermore, single case reports have been published.[4,5] In 1988, one group reported on eight patients with LGIOS and stressed the relevant radiographic features.[6]

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Materials and Methods

By the term LGIOS, we mean a cytologically well-differentiated (Broder Grade 1 and 2) osteosarcoma, in which the architectural features resemble fibrous dysplasia, desmoplastic fibroma, or parosteal osteosarcoma. Conventional osteosarcoma, however, is high grade (Grade 3–4).

Ten patients with LGIOS were identified from the Istituto Rizzoli files, which includes approximately 1000 cases of osteosarcoma. Clinical information, roentgenograms, and histologic slides were reviewed in all instances. Information as to the surgical treatment and follow-up was available in all except two patients.

Results

The significant clinical data on all 10 patients are reported in Figure 1. There were four men and six women (age range, 15–64 years; mean, 32.7 years at the time of diagnosis; Table 1). Six of these patients were in the second and third decades of life.

Long bones were the site of involvement in eight patients, and the knee area (distal femur, four patients; proximal tibia, two patients) was the preferred site. One patient had ischial involvement, and one had astragalar. Clinically, the symptoms were nonspecific. The lesions were painful in seven patients; the pain was followed by swelling in two. No symptoms were reported in the 10th patient who sustained a pathologic fracture 2 years before the diagnosis. The duration of symptoms

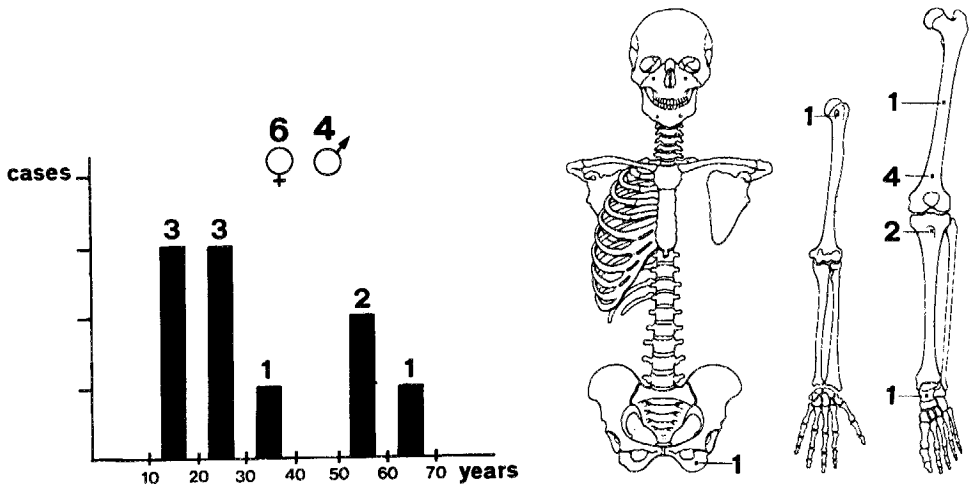


Figure 1. Distribution of LGIOS by patient age and lesion site.

before surgical biopsy or treatment ranged from 5–12 months (average, 10 months).

Radiographic Appearance

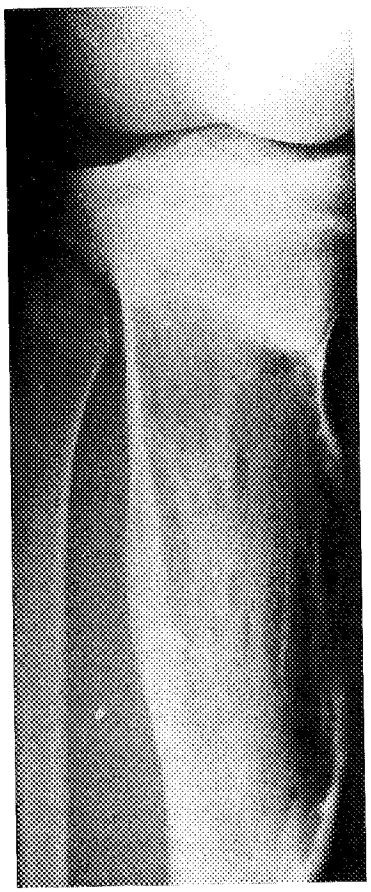
All tumors were in the medullary cavity. Four lesions involved the metaphysis and the epiphysis, three only the metaphysis, and one the diaphysis. There was no lesion that was purely epiphyseal. The last two patients had tumors located in the astragalus and the ischium, respectively.

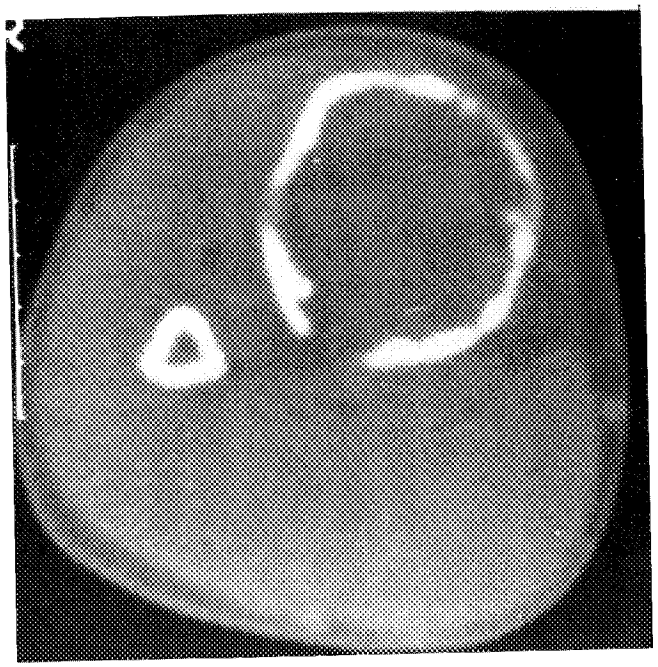
Five lesions had poor margination, three had sharp well-defined margins, and two had intermediate margins. Four lesions were entirely lytic, and two of these had small trabeculae (Figs. 2–3). A variable amount of matrix mineralization was present in six lesions. One of the latter showed pronounced increased density at the time of the first presentation. In this patient, serial radiographic studies detected a lesion that was completely sclerotic for 6 years, and then an appearance of patchy lucent areas followed. At the time of marginal resection, the lesion was partially lytic and partially sclerotic. At

Table 1. Clinical Data on 10 Patients With Low-Grade Intraosseous Osteosarcomas

Patient no.	Sex	Age (yr)	Symptom duration	Location	First treatment	Additional treatment	Follow-up (mo)
1	F	25	1 yr pain 3 mo swelling	Distal femur (meta-epiphysis)	Incisional biopsy and wide resection (3/90)	—	NED (16 mo)
2	M	50	5 mo pain	Distal femur (meta-epiphysis)	Incisional biopsy and wide resection (5/90)	—	NED (14 mo)
3	F	53	1 yr pain 8 mo swelling	Proximal tibia (meta-epiphysis)	Biopsy (10/81)	Marginal resection (11/88) Incisional biopsy (2/89) for LR AK amputation (2/89)	+5/89 (lung and liver metastases)
4	M	17	1 yr pain	Proximal tibia (metaphysis)	Incisional biopsy and wide resection (3/90)	—	NED (16 mo)
5	M	39	1 yr pain	Ischium	—	—	—
6	M	15	1 yr pain	Femur (diaphysis)	Incisional biopsy (9/85)	Curettage (9/86) Wide resection (10/89) after pathologic fracture	NED (21 mo)
7	F	21	1 yr pain	Distal femur (metaphysis)	Incisional biopsy and resection (6/89)	Mid thigh amputation (1/90)	NED (18 mo)
8	F	19	Pathologic fracture (2 yr ago)	Proximal humerus (metaphysis)	Incisional biopsy and wide resection (5/80)	—	NED (134 mo)
9	F	24	7 mo pain	Distal femur (meta-epiphysis)	—	—	—
10	F	64	6 mo pain	Astragalus	Incisional biopsy and mid leg amputation (5/79)		LR and lung metastases (9/81) + 5/82

NED: no evidence of disease; AK: above knee; LR: local recurrence.





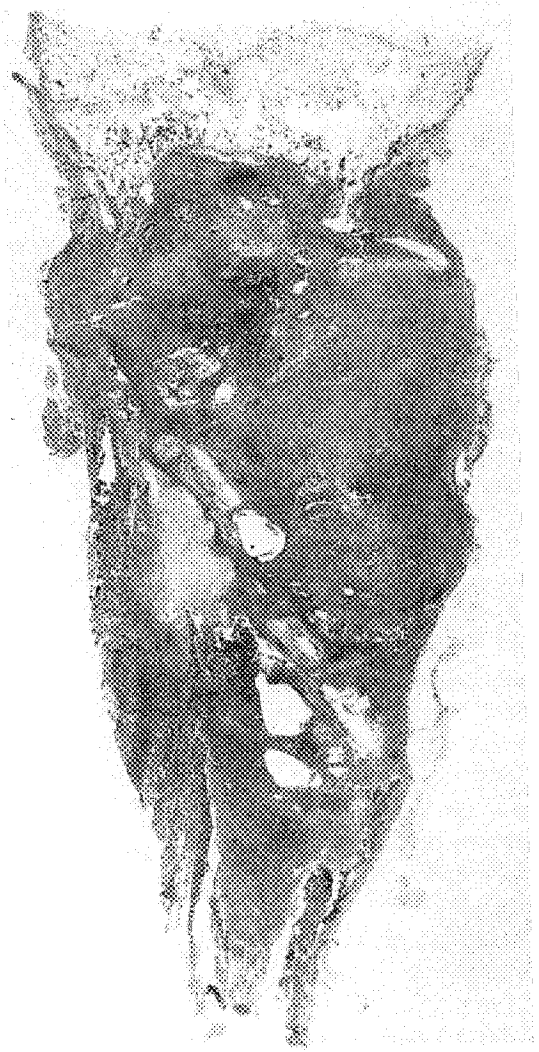
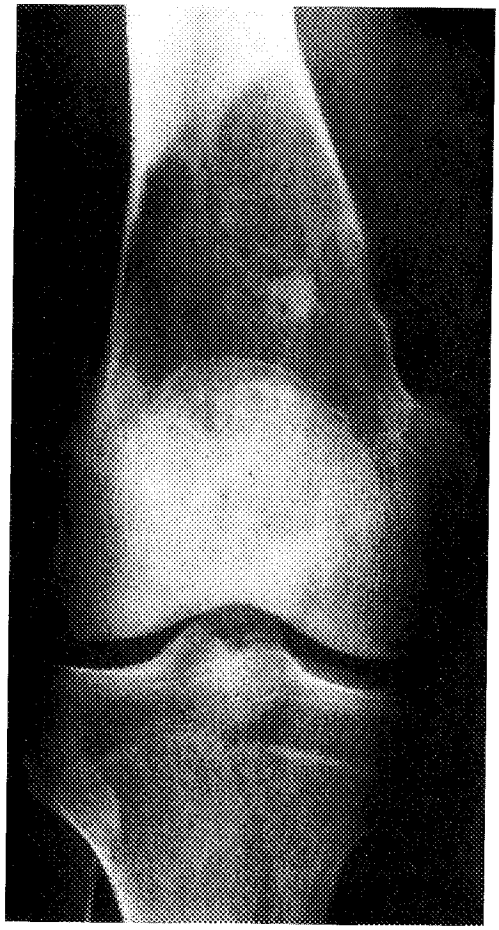
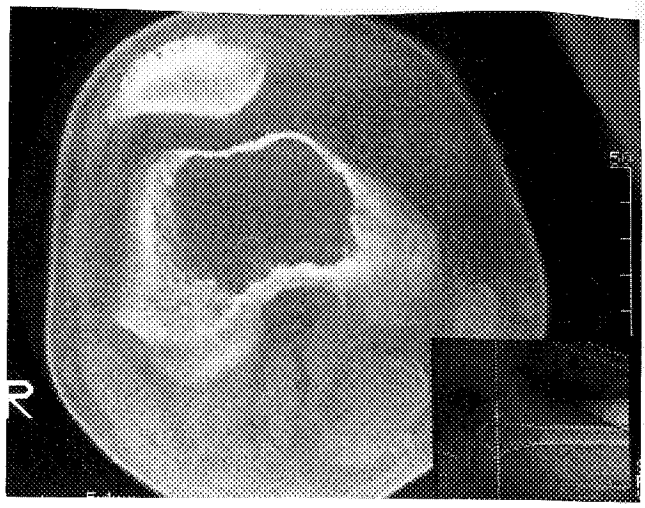
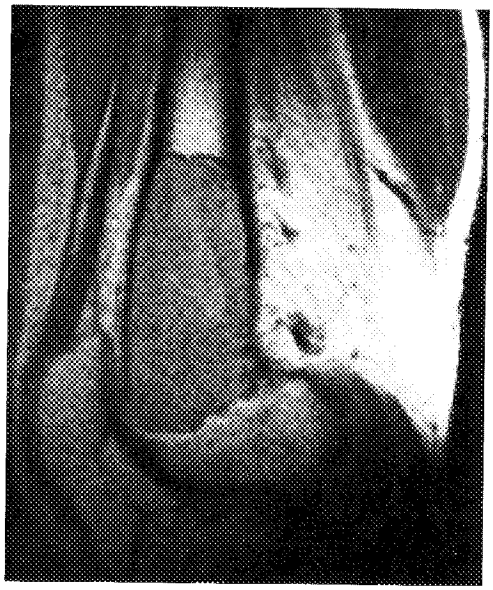


Figure 2. A large moderately trabeculated LGIOS, involving the metaphysis of the tibia, with cortical destruction and indistinct margins. Anteroposterior view and computed tomographic scan showed breakthrough to the cortex. Magnetic resonance imaging depicted breakdown of the cortex and intraosseous extension. All mounts confirmed the radiologic staging study (Patient 4).







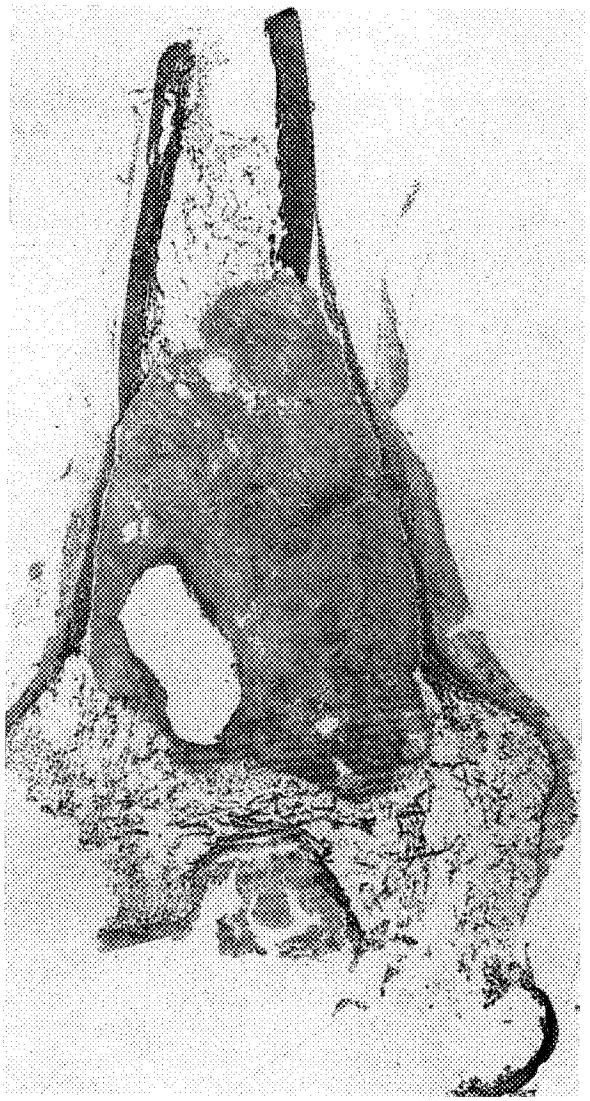


Figure 3. Anteroposterior view of a large LGIOS with cortical erosion and indistinct margins. Computed tomographic scan and magnetic resonance imaging showed the permeating margins and cortical bone erosion. The lesion extended to the metaphysis and epiphysis of the distal femur. All mounts confirmed the radiologic staging study (Patient 2).

that time, an area of dedifferentiation was identified histologically. Cortical destruction was detected in seven patients. In six, it was incomplete; in one, it was extensive and definite. In four instances, the lesions were expansive (Fig. 2). Extension into the soft tissue was identified in four patients. In another, there was invasion of the articular space.

Periosteal new bone formation was identified in five patients; it was in the form of laminated new bone in one and as linear spicules of bone radiating from a central point in the other four. In two of these, both linear radiating bone spicules and a Codman triangle were present. Pathologic fracture occurred in one patient. The surgical staging system (according to the Musculo-Skeletal Society) was Stage IA in three patients and IB in seven patients.[7] The size of the lesion at the time of the first presentation varied from $5 \times 4 \times 5$ cm to $15.5 \times 6 \times 6$ cm (average, $9.8 \times 5.8 \times 5.8$ cm). In summary, the radiographic appearance confirmed malignancy in five patients and suggested it in two others. There was a benign radiographic appearance in three cases.

Pathologic Features

Grossly, on the cut section, the lesions were well demarcated and had a variable appearance. Some appeared to be white, fibrous, and rubbery; others had a firm gritty aspect. Scattered red hemorrhagic areas were detected in three lesions.

Erosion of the endosteal cortical bone and cortical erosion or violation was detected in six instances. A soft tissue mass, either large and bulky (two lesions) or small and discrete (two lesions), was identified in four tumors. Histologic examination on a panoramic view showed a consistent pattern: bundles of spindle cells arranged in an interlacing pattern in a heavy collagenous background with bone or osteoid production.

Osteogenesis was minimal or heavily diffuse. Three lesions contained heavy bony trabeculae with a spindle cell stroma simulating the appearance of parosteal osteosarcoma. As in this lesion, the irregular bone trabeculae seemed to arise directly from the spindle cells. Two tumors had irregular bony seams in a spindle cell stroma simulating fibrous dysplasia. A "Chinese letter-like" appearance or "psammoma-like" bone formation was a feature of the bony trabeculae (Fig. 4).

In another two specimens, a prominent spindle cell proliferation was identified with scattered thin-walled gaping vessels and heavy collagenization as in desmoplastic fibroma of bone or in soft tissue aggressive fibromatosis (Figs. 5B and C). A small amount of osteoid production generally was present. There was a mixed histologic pattern in which the parosteal osteosarcoma-like aspect and the fibrous dysplasia-like aspect occurred together in two lesions. In one instance, the desmoplastic fibroma-like appearance was associated with the fibrous dysplasia-like aspect. Three tumors were considered Grade 1 and seven, Grade 2. In the Grade 1 lesions, the nuclei were relatively sparse and showed minimal hyperchromatism and variation in size and shape. Grade 2 lesions were characterized by areas of sparse nuclei fading into more cellular areas with slightly more pronounced (more than in Grade 1) hyperchromatism and variation in size and shape. Collagen among the tumor cells was prominent in Grade 1 and abundant in Grade 2. Chondroid differentiation occurred in four tumors. It was generally a minimal component: minute foci among the spindle cells or associated with bony trabeculae. The peripheral edge of the lesion had a consistent infiltrating pattern (Fig. 5A). It was possible to identify fatty bone marrow permeation in eight lesions. Minimal permeation between the peripheral host bony trabeculae or "entrapment" of the host trabeculae at the growing edge of the tumor was present in all specimens. Periosteal and cortex permeation was detected in seven lesions. In four of these, there was also soft tissue extension.

In two patients, the slides of the original lesion and the recurrence were available for study. In the first patient, the original histologic diagnosis was Paget disease and/or fibrous dysplasia. At the time of amputation 7 years later, there were areas of high-grade osteosarcoma (dedifferentiation). In the second patient, the original histologic diagnosis was fibrous dysplasia. The histologic features were unchanged in the bone and soft tissue recurrence 3 years later.

Treatment and Behavior (Table 2)

Initial treatment was intralesional curettage or marginal resection in three patients, marginal amputation in one, and wide resection in four. In two other patients, there was no information available about treatment. In the group of patients in whom intralesional curettage was done, all had recurrences requiring additional surgery. Of these, Patient 3 (Table 1) underwent marginal resection 7 years after the first biopsy. Three months later, after a local recurrence, an above-the-knee amputation was done; at this time, the tumor was Grade 4 osteosarcoma. She died 3 months later of metastatic disease. In the other two patients, one underwent a wide resection (after a recurettage) 4 years after the initial procedure; the other patient had a midthigh amputation 7 months after the initial treatment. Wide resection was done as the initial treatment in four patients. There was no recurrence, and all were alive without disease after an average interval of 45 months (range, 14–134 months). One patient underwent a marginal amputation as initial surgery. She died 3 years later with local recurrence and lung metastases.

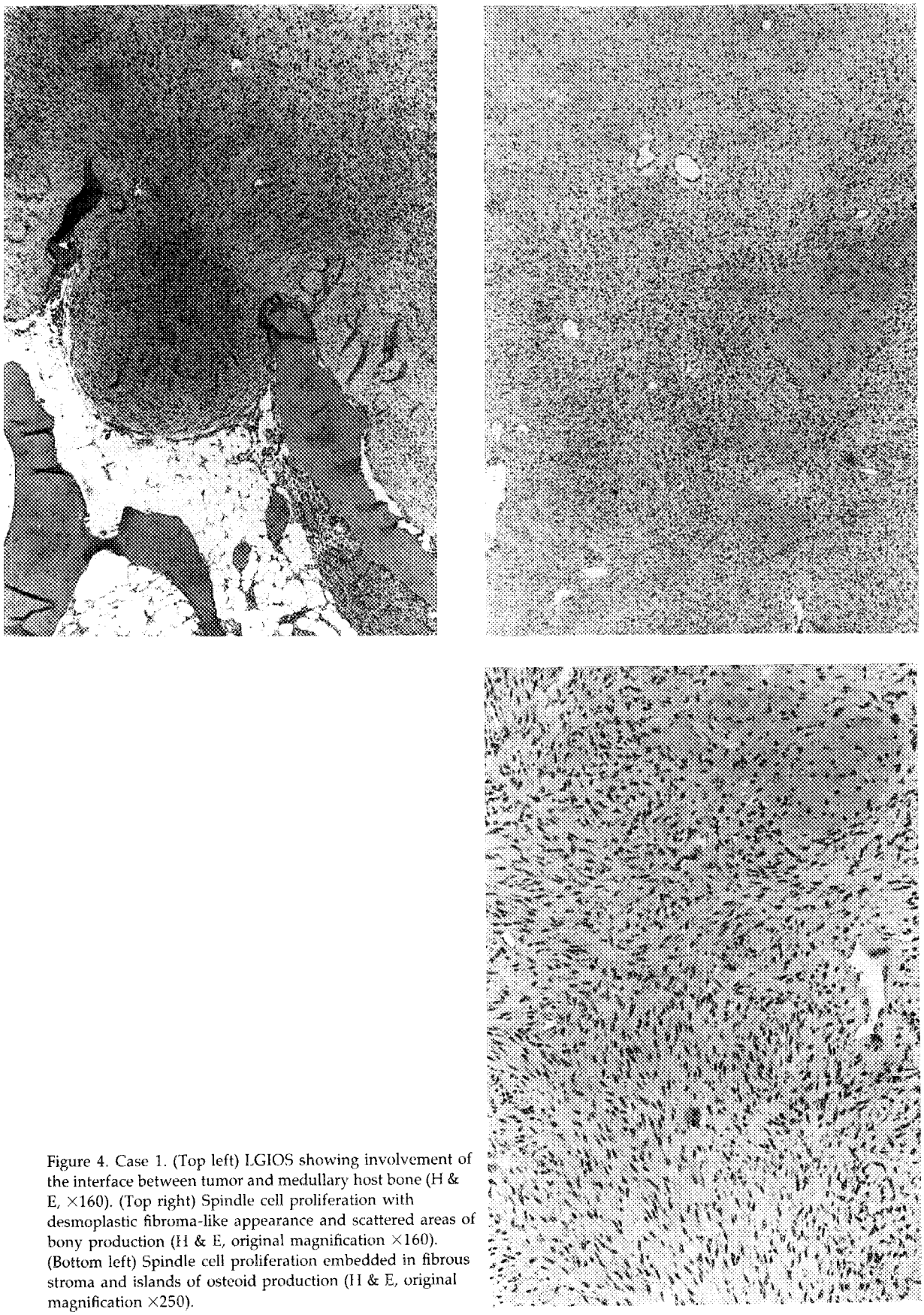


Figure 4. Case 1. (Top left) LGIOS showing involvement of the interface between tumor and medullary host bone (H & E, ×160). (Top right) Spindle cell proliferation with desmoplastic fibroma-like appearance and scattered areas of bony production (H & E, original magnification ×160). (Bottom left) Spindle cell proliferation embedded in fibrous stroma and islands of osteoid production (H & E, original magnification ×250).

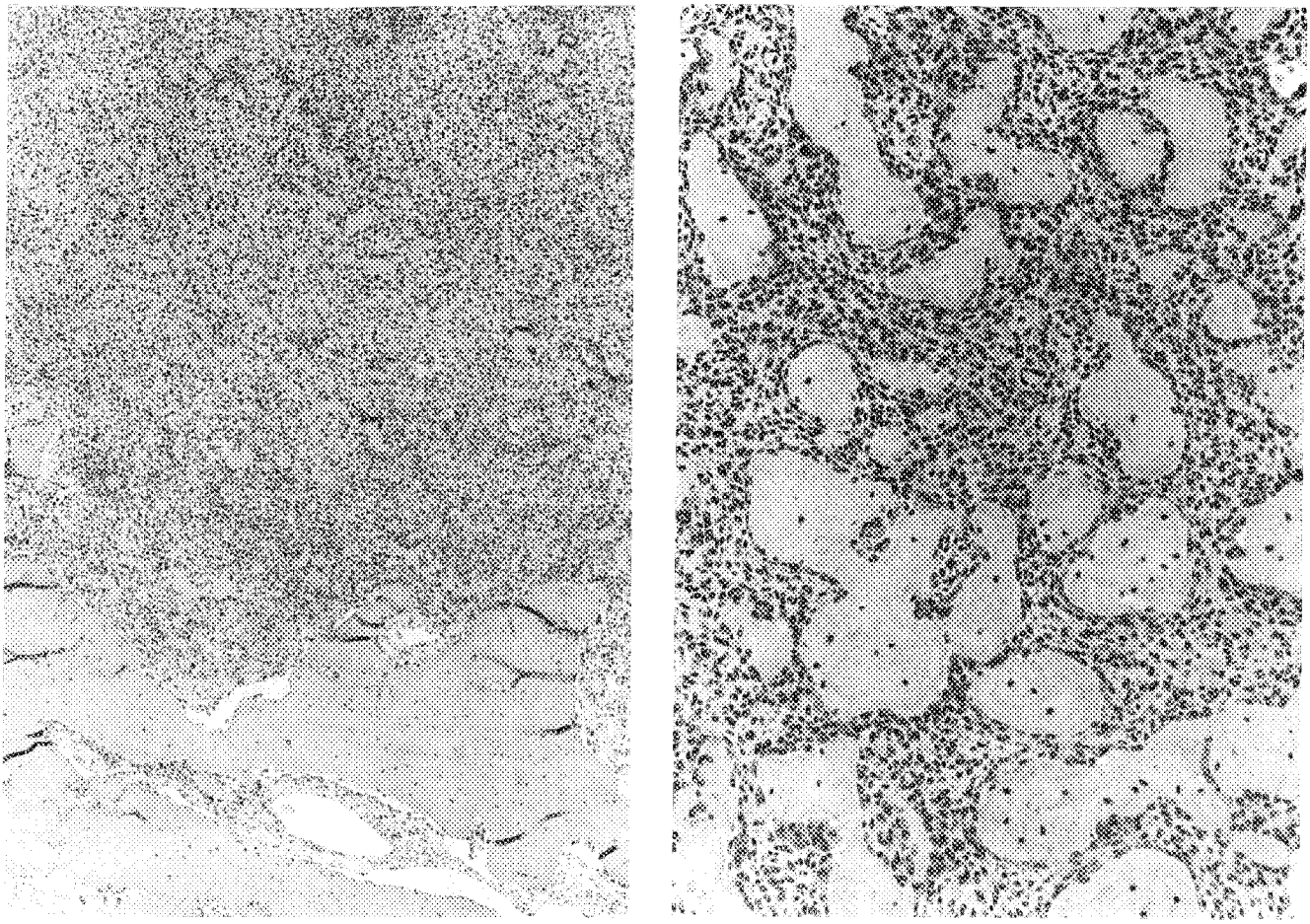


Figure 5. Case 6. (Left) Fibrous dysplasia-like LGIOS with invasion of the host trabeculae (H & E, original magnification ×160). (Right) Higher magnification in which spindle-shaped cells with indistinct borders encircled irregular or oval elongated trabeculae. The nuclei were hyperchromatic with minimal atypia (H & E, original magnification ×250).

Discussion

Currently, osteosarcoma is not considered a single disease but is divided into several different varieties according to clinical, radiographic, and histologic features. Even if most osteosarcomas are high grade, it is important to recognize low-grade osteosarcoma, both central and superficial.[2,3] The latter is the so-called parosteal osteosarcoma, which was reported extensively in the literature as having a good prognosis and being different from the "usual" osteosarcoma.[2,3] However, central (medullary) low-grade osteosarcoma (LGIOS) is

Table 2. Treatment and Behavior

Surgical treatment	No. of patients*	Recurrence	Treatment	Follow-up from the last treatment (from first diagnosis)
Intralesional curettage or marginal resection	3	1	AK wide amputation after a marginal resection	Dead after 3 mo with lung and liver metastases (7 yr, 7 mo)
		1	Wide resection after an intralesional curettage	NED after 21 mo (6 yr)
		1	Midthigh amputation after a marginal resection	NED after 18 mo (24 mo)
Marginal amputation	1	1	No treatment	Dead after 3 yr with LR and lung metastases
Wide resection	4	—	—	NED (average 45 mo)

NED: no evidence of disease; AK: above knee; LR: local recurrence.

* Two patients were lost at follow-up and no information was available about treatment.

rarer. In 1977, the cases 27 patients were reported.[8] A recent (1990) article from the same institution updated their experience with 80 cases of LGIOS: 16 from the Mayo Clinic files and 64 from consultation files.[1]

In our limited series of 10 patients, our results were similar. There were slightly more women than men, and the mean age was in the third decade of life (32.7 years). The tumor had a strong predilection for long bone extremities (80%). Radiographically, features suggesting the malignant nature were found in seven patients (minimal or moderate intramedullary extension, cortical violation, and soft tissue involvement). A benign lesion was suggested in three.

These results were similar to those in the Mayo Clinic series. LGIOS findings are characteristic histologically; they include spindle cell proliferation with variable osteoid production, low cellularity, low mitotic rate, and bland or minimal cytologic atypical features identified to various degrees. Some peculiar growth patterns simulating parosteal osteosarcoma (three patients), fibrous dysplasia (three), and desmoplastic fibroma (two) were detected. Similar histologic features were described in the Mayo Clinic series. Moreover, a fibromyxoid appearance was reported in two patients.

In the original description of this osteosarcoma variety, only Broder Grade 1 lesions were considered.[8] We also included Broder Grade 2 lesions among the LGIOS we studied. In accordance with the Musculo-Skeletal Tumor Society staging and grading system, Grade 1 and 2 sarcomas are considered low grade.[7] The behavior of these tumors, at least in this small series, supported this concept. The absence of pronounced cytologic atypia of the cells and the presence of an infiltrating growing tumor edge were helpful in differentiating low-grade osteosarcomas from similar benign spindle cell bone lesions, such as fibrous dysplasia, aneurysmal bone cyst with prevalent solid component, desmoplastic fibroma, and nonossifying fibroma.

Occasionally, during histologic examination of a tiny biopsy specimen or fine-needle aspiration biopsy sample, the differential diagnosis between fibrous dysplasia and LGIOS can be difficult or even impossible to make. However, with roentgenograms, "fibrous dysplasia never has the appearance of malignancy."[1]

Two low-grade malignant lesions of bone can simulate the histologic findings of LGIOS: low-grade parosteal osteosarcoma and low-grade fibrosarcoma. Histologically, there may be a complete overlap between the morphologic features of LGIOS and low-grade parosteal osteosarcoma. Roentgenography will differentiate these two lesions, one in the central bone and the other on the surface. Low-grade fibrosarcoma, even if similar in spindle cell proliferation, lacks the osteoid or bony production characteristic of osteosarcoma. In only one of our patients was there progression of malignancy between the first and the second biopsy done 7 years apart. This patient had an aggressive clinical course with local recurrence and lung metastases and died 6 months after the detection of the upgrade, thus confirming that the clinical course was similar to that of patients with conventional high-grade osteosarcomas. The development of metastases was correlated with the progression of the histologic grade of malignancy into a high-grade conventional osteosarcoma. Two patients in the Mayo Clinic series[1] and one in the other series[2] had metastases from low-grade osteosarcomas. We found that treatment with intralesional or marginal surgical procedure always was followed by recurrence. Resection of this tumor with wide surgical margins is the treatment of choice. Chemotherapy was not used and does not seem indicated unless dedifferentiation occurs.

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